Miniature Flow Cytometer

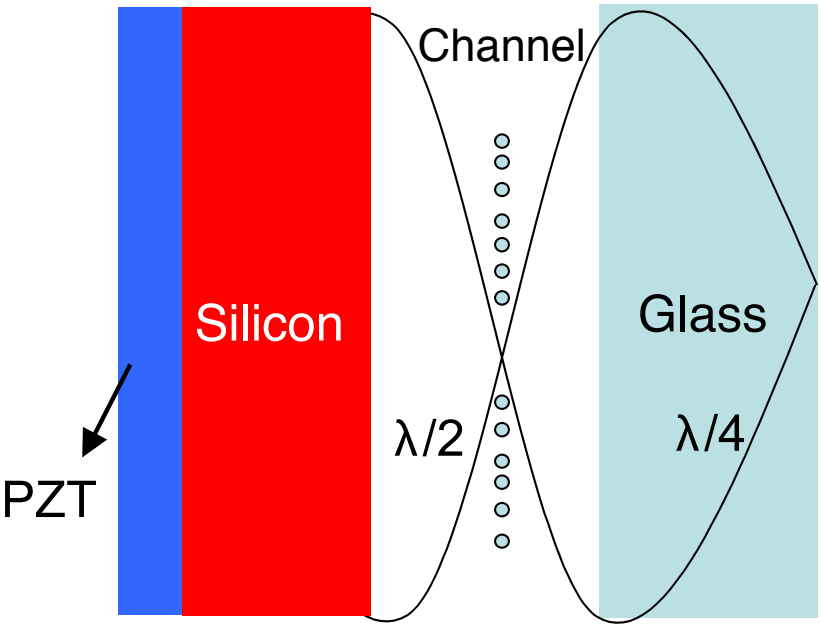

Figure 1: Schematic of the miniature flow cytometer concept, illustrating how acoustic standing waves (wavelength λ) are used to control particle position within a micromachined microchannel. When the piezoelectric acoustic transducer (PZT) is turned on, flowing beads or cells move to the center of the channel where there is an acoustic pressure node.

Acoustic focusing is used to control particle position within microchannels

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Since the 1970s, flow cytometry has been a cornerstone technology in both research and in clinical diagnostics, particularly of infectious diseases. It is based on the hydrodynamic focusing of streams of microscopic particles (cells or microbeads) that are interrogated using laser-induced fluorescence. Flow cytometry instruments are complex, bulky and expensive, and for many years there has been extensive research into portable alternatives, primarily using microfluidics. The latter is a very appealing solution since it relies on microfabrication and, in principle, allows for the integration of the required optics and electronics into one chip. However, extending hydrodynamic focusing to microfluidic environments is not viable because: 1) It is very difficult to create a capability for three-dimensional hydrodynamic focusing in a geometry compatible with microfabrication. 2) It requires a large amount of sheath liquid, thus limiting the portability and potentially generating an equivalent volume of hazardous waste. 3) This effect works only at high flow speeds which in turn increases the cost and complexity of the optics and electronics.

An alternative to hydrodynamic focusing pioneered by Los Alamos National Laboratory and others is to use acoustic wave forces on the flowing particles (or cells) and confine them to a single flow line. An ultrasound standing wave field will move suspended particles toward either the pressure nodes or the pressure antinodes depending on the density and compressibility of the particles and medium (Fig. 1). The coupling of the acoustic force to the entire microfluidic platform also allows it to span hundreds of micron-sized fluidic channels simultaneously. Moreover, the forces can be spatially decoupled to strengthen primary radiation forces in one dimension and reduce those in other directions.

As shown schematically (cross-section) in Figure 1, Sandia researchers have recently demonstrated acoustic focusing of flowing

particles in a silicon microfluidic chip with performance sufficient to satisfy most flow cytometry applications. A piezoelectric transducer (PZT) is integrated with a silicon microchannel of square cross section and low roughness. The microfluidic channel and corresponding through-wafer ports were fabricated using a two-step deep reactive ion etching process. The channel dimensions (~210 µm width and height) were chosen such that they set up acoustic standing waves of one-half wavelength both laterally and vertically within the cavity when actuated at 3.5 MHz.

A key aspect of this accomplishment was the development of a 2-D finite element model to predict both the location and strength of the acoustic nodes in the microchannel. The model is a dramatic improvement over prior work in that an accurate prediction of the focusing behavior is now possible. Unlike previous analytic models that are extensions of one-dimensional models, this approach captures the acoustic coupling in both the lateral and vertical directions to reveal the nodal behavior as a function of the model parameters such as input frequency. This model has been used to aid in analysis and improvement of device performance. Typical performance of such devices is shown in Fig. 2 where acoustic focusing occurs both laterally and vertically.

The reduced cost and simplification of operation of a miniature flow cytometer will enable the system to be fielded in clinical settings around the world, especially in remote locations and combat environments where trained technicians are unavailable. This would greatly increase the potential for early detection and diagnostics of pathogens, both endemic to a population and those deriving from bioterrorism.

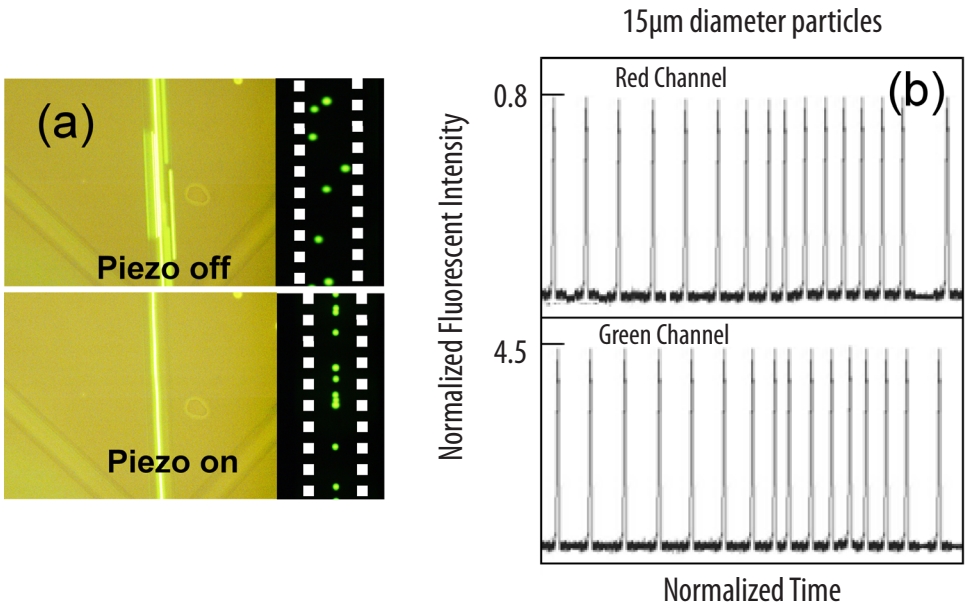

Figure 2: (a) A micrograph showing fluorescent beads when the acoustic transducer is turned on and off; (b) Uniform fluorescence intensity of two-color fluorescent beads flowing under acoustic focusing. Each spike corresponds to one bead passing through the laser beam.

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